

REMARKS

A check for the requisite fees for a three month extension of time and for filing a Request for Continued Examination (RCE) accompanies this response. Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of Time is needed, this paper is to be considered such Petition, and any fee charged to Deposit Account No. 06-1050.

Claims 1 and 3-7 are pending in this application. Claims 6 and 7, which have been withdrawn from consideration as drawn to subject matter allegedly non-elected by original presentation, are so-indicated, but are retained. Claim 7 is amended to be consistent with claim 1. It respectfully is submitted that, since these claims ultimately depend on claim 1, they will allowable if claim 1 is determined to be allowable. Hence, they are retained for possible rejoinder upon allowance of claim 1. Claims 8-10, which also are deemed withdrawn as drawn to subject matter non-elected by original presentation are cancelled without prejudice or disclaimer. Applicant reserves the right to file divisional/continuation applications to the non-elected subject matter.

Claim 1 is amended herein for clarity. Basis for the amendment to claim 1 can be found, for example, in original claim 2, and throughout the specification, for example, at page 5, lines 4-10; at page 5, line 17-21; at page 9, lines 9-14; and at page 10, lines 9-13. Therefore, no new matter is added.

I. THE REJECTION OF CLAIMS 1 and 4-5 UNDER 35 U.S.C. §102(e)

Claims 1 and 4-5 are rejected under 35 U.S.C 102(e) as anticipated by U.S. Patent No. 5,785,970, which discloses a method of treating of a gastro-intestinal disorder by administering to a mammal a therapeutically effective amount of an anti-G17 immunogen. The Examiner urges that the method of the prior art comprises the same method steps as the instant claims, which include administering a therapeutically effective amount of an anti-G17 immunogenic composition to subjects suffering from gastrointestinal tumors for the treatment of gastrointestinal tumors. Hence, the Examiner concludes that the claimed method is anticipated because the method will inherently lead to the treatment of gastrointestinal tumors whose growth is stimulated by glycine-extended gastrin-17 and will inherently lead to inhibiting the physiological activities of gastrin-17 and glycine-extended gastrin-17 and/or amidated gastrin-17. . This rejection respectfully is traversed.

Summary of arguments below

U.S. 5,785,970 does not disclose all elements **as claimed**. U.S. 5,785,970 does not disclose the treatment of gastrointestinal tumors that express glycine-extended gastrin-17, nor a method in which an amount of anti-G17 immunogen that is administered must be sufficient to neutralizes gastrin-17 **and** glycine-extended gastrin-17, which would be in excess of the amount required just to inhibit gastrin-17. Furthermore, not all gastrointestinal tumors express glycine-extended gastrin-17; hence, the population of patients treated is different. Applicant also rebuts below some of the Examiner's assertions.

Relevant law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S., 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). It is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik GmbH v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

The Rejected Claims:

Independent claim 1 is directed to a method for the treatment of a gastrointestinal tumor including the step of:

administering to a mammal a therapeutically effective amount of an anti-G17 immunogenic composition, wherein:

the gastrointestinal tumor *expresses glycine-extended gastrin-17*; and
the amount of the immunogenic composition administered is sufficient
to induce an anti-gastrin-17 antibody titer to neutralize gastrin-17 and
glycine-extended gastrin-17.

Dependent claims recite particulars of the tumors or method. All of the claims, thus, require that the method is for treatment of tumors that express glycine-extended gastrin-17. In

addition, all claims require that the amount of the immunogenic composition administered is sufficient to generate antibodies to **neutralize gastrin-17 and glycine-extended gastrin-17**. Accordingly, the claims require that the anti-G17 immunogenic composition is one that is capable of generating antibodies to gastrin-17 and glycine-extended gastrin-17.

As described in the application, *some* anti-G17 immunogens generate antibodies not only to G17, but also to the glycine-extended gastrin-17 and/or amidated gastrin-17. As recognized by Applicant, such anti-G17 immunogens can be used in the treatment of cancers that are trophic due to expression of these precursor hormones. Further, as disclosed in the specification, the amount of the immunogenic composition is one that elicits antibody titers to neutralize gastrin-17 **and glycine-extended gastrin-17**. The specification states as follows:

The antibody titers raised by the anti-G17 immunogens are *in excess* of those required to neutralize serum G17 resulting in high serum levels of uncomplexed antibodies which are free to bind to G17-Gly. Thus, the 'free' serum-associated antibodies would be available to neutralize cell-associated G17 peptides in well-vascularized areas of the tumors. [Emphasis added]

Hence, an anti-G17 composition that is capable of eliciting antibodies to gastrin-17 is not necessarily capable of eliciting antibodies to glycine-extended gastrin-17. Further, an amount of anti-G17 composition to induce an anti-gastrin-17 antibody titer to gastrin-17 and glycine-extended gastrin-17 is not the same as an amount that is sufficient to induce an anti-gastrin-17 antibody titer sufficient to neutralize gastrin-17 **and glycine-extended gastrin-17**.

Differences between the disclosure of U.S. Patent No. 5,785,970 and the rejected claims

U.S. Patent No. 5,785,970 discloses methods for treating tumors by administering immunogenic compositions for passive or active immunization that are selective against gastrin-17. U.S. Patent No. 5,785,970 discloses anti-G17 immunogens that elicit antibodies having specificity for G17, but not G34. U.S. Patent No. 5,785,970 discloses a method in which a sufficient titer of antibodies is induced by such anti-G17 immunogens to inhibit binding of gastrin-17 to its receptor on the tumor, while not being cross reactive with G34. U.S. Patent No. 5,785,970 discloses treatment of tumors with these immunogens.

U.S. Patent No. 5,785,970 does not disclose that anti-G17 immunogens induce an anti-gastrin-17 titer sufficient to neutralize gastrin-17 **and glycine-extended gastrin-17**. U.S. Patent No. 5,785,970 does not disclose treatment of tumors that express glycine-extended gastrin-17. U.S. Patent No. 5,785,970 also does not disclose treatment of tumors that express glycine-

extended gastrin-17, nor treatment tumors with anti-G17 immunogens to tumors that are trophic due to this precursor hormone. U.S. Patent No. 5,785,970 also does not disclose administering an amount of anti-G17 immunogens that is capable of eliciting antibodies against gastrin-17 and glycine-extended gastrin-17. Hence this patent does not disclose methods for treatment of tumors that express these molecules, nor methods that include administering an amount of an immunogenic compositions sufficient to inhibit physiological effects of gastrin 17 and glycine-extended gastrin-17 to effect treatment of the tumor. Accordingly, U.S. Patent No. 5,785,970 does not disclose all elements *as claimed* and does not anticipate any of claims 1 and 4-5.

Rebuttal to Examiner's Arguments

1) The Examiner urges that the claimed method is anticipated because the method of US. Patent No. 5,785,970 will inherently lead to inhibiting the physiological activities of gastrin-17 and glycine-extended gastrin-17. This is not correct.

As noted above, it is applicant, not the cited reference that discloses that anti-G17 immunogens are capable of inhibiting and neutralizing the effects of glycine-extended gastrin-17 for the treatment of tumors stimulated by such a hormone. The claims recite that the amount immunogen required to neutralize the effects of G17 and glycine-extended gastrin-17 is an amount capable of generating an antibody titer in *excess* of that needed to inhibit gastrin-17 alone. Example 1 exemplifies this. Example 1 and Figure 1 demonstrate that the inhibitory concentration of antisera obtained from animals immunized with the anti-G17 immunogen G17(1-9)DT for displacement of ¹²⁵IG17 by gastrin-17 and glycine-extended gastrin-17 was IC₅₀ of 3500 pg/ml and IC₂₅ of 12,000 pg/ml, respectively. Thus, the antibodies generated from this immunogen preferentially bind gastrin-17 over glycine-extended gastrin-17, and a higher concentration of antibody is required to inhibit glycine-extended gastrin-17. Thus, an amount of immunogen that elicits a sufficient titer of antibodies that neutralize gastrin-17 **would not be** sufficient to induce a sufficient titer of antibodies to neutralize gastrin **and** glycine-extended gastrin-17.

Furthermore, as described in the application not all tumors that express G17, also express glycine-extended G17. Thus, the instantly claimed method is for treating a different patient population than the population treated in the cited patent, which discloses generic methods for treating tumors.

Therefore, the instantly claimed method is not inherent in the method of U.S. Patent No. 5,785,970.

2) The Examiner urges that "the claimed method appears to be the same as the prior art method, absent a showing of *unobvious* differences." It is respectfully submitted that this is not the correct standard to use for anticipation. Anticipation requires that the prior art reference disclose each element of the instantly claimed method as claimed. As discussed above, U.S. patent 5,785,970 does not disclose all elements as claimed.

If the Examiner wishes to make a rejection that instantly claimed methods are obvious, such a rejection should be made under 35 U.S.C. §103(a) to provide Applicant an opportunity to address the rejection. Nevertheless, Applicant respectfully submits that the claimed method is not obvious in view of U.S. Patent 5,785,970. U.S. Patent 5,785,970 does not teach or suggest the species of glycine-extended gastrin-17 or amidated gastrin-17, nor that such hormones are capable of being neutralized by an anti-G17 immunogen. Further, U.S. Patent 5,785,970 discloses that such anti-G17 immunogens *specifically and selectively* neutralize G17. U.S. Patent No. 5,785,970 does not teach a method in which an amount of immunogen is administered that is sufficient to induce sufficient a sufficient titer of antibodies to neutralize gastrin-17 and glycine-extended gastrin-17. There is no disclosure, teaching or suggestion in U.S. Patent No. 5,785,970 to modify its methods so that, for tumors that express extended glycine-G17 the amount of immunogen is adjusted to elicit a titer of antibodies to neutralize glycine- extended G17 **and** G17. Hence there is no teaching or suggestion in U.S. Patent No. 5,785,970 to do that which applicant has done. The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); see, also, *In re Papesh*, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963). Hence the instantly claimed methods are not obvious over U.S. Patent 5,785,970.

II. REJECTION OF CLAIMS UNDER 35 U.S.C. §112 – ENABLEMENT

Claims 1, 3-5 are rejected under 35 U.S.C. §112, first paragraph for two reasons discussed below. Applicant's response to each is set forth in turn below, following preliminary remarks and an outline of the relevant law regarding the enablement requirement of 35 U.S.C. §112, first paragraph.

Preliminary Remarks

The Examiner's statement in both enablement rejections that "one cannot extrapolate the teachings of the specification to the enablement of the claims" is a misstatement of the standard for enablement. To satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, the specification must teach one of skill in the art to make and use the subject matter as claimed without undue experimentation. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Accordingly, the teachings of the specification is only one factor in an enablement determination.

Hence, a consideration of the factors enumerated in In re Wands, including the scope of the claims, the teachings and examples in the specification for assessing expression of glycine-extended gastrin-17 and administering an amount of immunogen sufficient to inhibit the various gastrin forms, the high level of skill of those in this art, the advanced knowledge of those of skill in the art, the fact that it is predictable given the extensive teachings of the instant application and the state of the art at the time of the effective date of the claims, it would not require undue experimentation for one of skill in the art to make and use the methods as claimed herein.

Relevant law

To satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be met by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything within the scope of a broad claim." In re Anderson, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of §112, first paragraph "can be fulfilled by the use of illustrative examples or by broad terminology." In re Marzocchi et al., 469 USPQ 367 (CCPA 1971)(emphasis added).

Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." *In re Grimme, Keil and Schmitz*, 124 USPQ 449, 502 (CCPA 1960). Thus, there is no doubt that a patentee's invention may be broader than the particular embodiment shown in the specification. A patentee not only is entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. *Smith v. Snow*, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935).

Thus, there is no requirement for disclosure of every species within a genus. Applicant is entitled to claims are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed.

The scope of enablement is based on that which is disclosed in the specification plus the scope of what would be known to one of skill in the art without undue experimentation.

National Recovery Technologies, Inc. v. Magnetic Separation Systems, Inc., 166 F. 3d 1190, 49 USPQ 2d 1671 (Fed. Cir. 1999). A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). Hence all that is known to those of skill in the art is part of the disclosure of the application.

To establish a *prima facie* case of lack of enablement, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for what is claimed. *In re Wright*, 999 1557, 1561-62, 27 1510, 1513 (Fed. Cir. 1993). (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). See also *Morehouse*, 545 162, 192 USPQ 29 (CCPA 1976). The inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require undue experimentation to make and use the subject matter *as claimed*. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or

guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'l 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). All factors must be considered. A deficiency in meeting some factors does not preclude a finding of enablement. Consideration of a few factors is **not** dispositive.

A. THE REJECTION OF CLAIMS 1 and 3-5 UNDER 35 U.S.C. §112, FIRST PARAGRAPH - ENABLEMENT

Claims 1, 3-5 are rejected under 35 U.S.C. §112, first paragraph because it is alleged that the specification does not reasonably provide enablement for the subject matter as claimed. It is alleged that those of the art recognized that the action of glycine-extended gastrin-17 on gastrointestinal tumors could not be predicted, and that one could not predict with a reasonable expectation of success whether or not glycine-extended gastrin-17 in fact stimulated gastrointestinal tumors based on either the teaching in the specification or the art of record. Further, the Examiner urges that because the art of anticancer drug discovery for cancer therapy is highly unpredictable, in the absence of experimental evidence in an appropriate animal model, with data commensurate in scope with the claims, no one skilled in the art would accept the assertion that the claimed method would function as claimed based only upon the hypothesis that serum-associated G17 has the potential to stimulate the growth of colorectal tumors in an endocrine manner mediated by CCKB receptors. This rejection is respectfully traversed.

First, it is respectfully submitted that this rejection is moot in view of the amendment to claim 1 herein. The amendment is made herein to clarify the nature of the claimed subject matter and to advance prosecution of the instant claims. As amended the claims recite that treatment is for tumors that express glycine-extended G17. As discussed below, the specification clearly teaches how to identify such tumors and also how to determined dosage for treatment of such tumors.

Notwithstanding this, Applicant respectfully submits that the specification sufficiently enables the claims as amended, i.e. to a method of treating a subset of gastrointestinal tumors that *express* glycine-extended gastrin-17 by administering anti-G17 immunogens in an amount that is sufficient to neutralize gastrin-17 and glycine-extended gastrin-17. The application teachings that anti-G17 immunogens can be used to target glycine-extended gastrin-17 when

used in a sufficient amount, and that by virtue of this, tumors that express glycine-extended gastrin-17 can be treated to prevent the trophic effects of this precursor hormone. The effects of the glycine-extended gastrin-17 were known at the time of filing the instant application.

In view of an analysis of the Wands factors, which is detailed in the second enablement rejection below, Applicant submits that there is no undue experimentation required to practice the method as claimed. Therefore, in light of the scope of the claims, the teachings in the specification, including methods to test for gastrointestinal tumors expressing glycine-extended gastrin-17, the knowledge of one of skill in the art, including the fact that glycine-extended gastrin-17 was known to be expressed in a subset of varied gastrointestinal tumors and method of testing for such expression in tumors generally, the high level of skill in the art, the predictability, and the nature of the claimed subject matter, it would not require undue experimentation to practice the methods as claimed.

Rebuttal to Examiner's Arguments

The Examiner alleges that one cannot extrapolate the teachings of the specification to the enablement of the claims due to the unpredictability of cancer therapy. The Examiner urges that in the absence of experimental evidence in an appropriate animal model, with data commensurate in scope with the invention claimed, no one skilled in the art would accept the assertion that the claimed method would function as claimed based on the hypothesis that serum-associated G17 has the potential to stimulate the growth of colorectal tumors in an endocrine manner mediated by CCK-B receptor. First, it is noted that the Examiner is alleging inoperability, which is an issue that should be raised under 35 U.S.C. §101. A rejection for lack of enablement under 35 U.S.C. §112, first paragraph, where the specification teaches how to make and use a produce and practice a claimed method, must be predicated on a rejection under 35 U.S.C. §101. No rejection under 35 U.S.C. §101 is set forth. This portion of the enablement rejection addresses lack of utility under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

The USPTO has released “Guidelines for Examination of Applications for Compliance with the Utility Requirement” [guidelines, which address utility under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph] and an “Overview of Legal Precedent Governing the Utility Requirement” [legal overview] to support the guidelines. Under section I.B.4. of these guidelines Examiners are reminded that:

They must treat as true credible statements made by an applicant or a declarant in the specification or in a declaration provided under 37 CFR §1.132, unless they can show that one of ordinary skill in the art would have a rational basis to doubt the truth of such statements.

Further, the legal overview provided by the USPTO, in section II.B.1., explains that:

[a]n applicant's assertion of utility creates a presumption of utility that will be sufficient, in most cases to satisfy the utility requirement of 35 U.S.C. §101..... To overcome the presumption, the *Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility*. In other words, the Examiner must show that the asserted utility is not credible. [Emphasis added; see e.g., *In re Langer* 503 F. 2d 1380, 183 USPQ 288 (CCPA 1974)].

The legal overview goes on to explain, in section II.B.2., when an asserted utility is not “credible”:

To assess credibility, the Examiner should determine if one of ordinary skill in the art would consider the assertions of the applicant to have any reasonable scientific basis. If they do, they should not be challenged as not being credible. Only where they do not [e.g., if the assertion is “incredible in view of contemporary knowledge”], should the Examiner challenge the statement as not being credible.

Thus, the Examiner must accept as true any credible statement of utility made by the Applicant and may only challenge the statement upon a showing that those of skill in the art would consider the assertion to *have no reasonable scientific basis*.

Further there is no requirement that the utility of a pharmacologically active substance be proven by *in vivo* testing. *In re Isaacs*, 146 USPQ 193, 195 (CCPA 1965). *In vitro* tests can raise the presumption of *in vivo* utility of the claimed compounds. "A standard *in vitro* test may be sufficient to demonstrate pharmacological activity of a compound." *Bigham v. Godtfredsen*, 222 USPQ 632, 637 (Bd. Pat. App. & Int'l. 1984), see, also *Nelson v. Bowler*, 206 USPQ 881, 883 (CCPA 1980); and *Cross v. Iizuka*, 224 USPQ 739, 741 (Fed. Cir. 1985).

With respect to pharmacological and therapeutic utilities, the legal overview provided by the USPTO, in section I.C., interprets *Nelson v. Bowler* as establishing the following:

"Knowledge of the pharmacological activity of any compound is *obviously beneficial to the public*. It is inherently faster and easier to combat illnesses and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities. Since *it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible*, we conclude that adequate proof of any such activity

constitutes a showing of practical utility. These general principles are **equally applicable to situations where an applicant has claimed a process for treating a human or animal disorder.**" (Emphasis added.)

The legal overview addresses the analysis of "credibility" of such utilities, in section II.B.2., as follows:

Special care should be taken when assessing the credibility of an asserted therapeutic utility for a claimed invention. In such cases, *a previous lack of success in treating a disease or condition, or the absence of a proven animal model for testing the effectiveness of drugs for treating a disorder in humans, should not, standing alone, serve as a basis for challenging the asserted utility under §101.*" (Emphasis added.)

Finally, the USPTO, in its legal overview, addresses some special considerations regarding asserted therapeutic or pharmacological utilities (Section III.) stating:

The Federal courts have consistently reversed rejections by the Office asserting a lack of utility under §101 for inventions claiming a pharmacological or therapeutic utility where an applicant has provided evidence supporting such a utility. In view of this, Examiners should be particularly careful in their review of evidence provided in support of an asserted therapeutic or pharmacological utility."

Thus, where a credible pharmacological utility is asserted by an applicant, it must be assumed by the Examiner to be a true statement of utility unless the Examiner shows that one of skill in the art would find no rational scientific basis for the asserted utility.

Notwithstanding this, Applicant submits that the Working Examples do provide data commensurate in scope with the claims. The data include data from *in vitro* tumor cell data and *in vivo* animal models known to those of skill in the art to demonstrate the efficacy of anti-tumor compounds. There is nothing of record to suggest that data from these *in vivo* and *in vitro* models are not sufficient to evidence the claim compounds function as described sufficiently to satisfy 35 U.S.C. §112, first paragraph and also 35 U.S.C. §101. The data is sufficient to meet the standard set forth in Nelson v. Bowler:

"Knowledge of the pharmacological activity of any compound is *obviously beneficial to the public*. It is inherently faster and easier to combat illnesses and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities. Since *it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible*, we conclude that adequate proof of any such activity constitutes a showing of practical utility. These general principles are **equally applicable to situations where an applicant has claimed a process for treating a human or animal disorder.**" (Emphasis added.)

The specification, including the Examples, demonstrate that the methods as claimed operate as claimed. Further, as discussed below, the specification teaches how to select dosages for treatment of tumors that express glycine-extended gastrin G17 and also how to identify such tumors. The Examples demonstrate practice of the claim methods by administration of an anti-G17 immunogen (via active immunization) to animals implanted with DHDK12 cells. Such animals serve as a model for a colon/colorectal tumor that expresses glycine-extended gastrin-17. This is a standard animal tumor model. The Examiner has provided evidence to doubt its use therefor.

Example 1 depicts expression of glycine-extended gastrin-17 in the DHDK12 cell line. Example 2 demonstrates that treatment of those cells *in vitro* with an anti-G17 immunogen results in a reduction in the levels of glycine-extended gastrin-17 to levels that were undetectable by the radioimmunoassay procedure using antibodies specific for glycine-extended gastrin-17. Example 3 demonstrates that rats implanted with DHDK12 tumors, when administered anti-G17 immunogens, had decreased growth of the tumors compared to those administered with a control treatment. Example 4 shows results of the assessment of *in vivo* antibody titers elicited by the anti-G17 immunogen when administered to the rats implanted with the DHDK12 tumors. The results show that the antibody titers elicited were in excess of that able to bind to gastrin-17, and that there was free anti-G17(1-9)DT antibody levels measured, which increased with successive immunization with the immunogen. This Example demonstrates that the amount of the anti-G17 immunogen administered was sufficient to generate antibody titers in excess of that able to bind gastrin-17, and that the antibody levels elicited could be controlled and monitored following further immunizations. Examples 6 and 7 depict analysis of expression of the CCK-B receptor on the DHDK12 tumors by immunocytochemical evaluation using a polyclonal serum to the CCK-B receptor. The results show that the DHDK12 tumors have a high level of expression of the CCK-B receptor. Thus, the specification provides data that demonstrate *in vivo* animal models that the methods are effective for treating gastrointestinal tumors that express glycine-extended gastrin-17 by administering to a an amount of an anti-G17 immunogenic composition sufficient to induce an anti-gastrin-17 antibody titer to neutralize gastrin-17 and glycine-extended gastrin-17. Such data is sufficient to evidence that the instantly claimed methods function as claimed.

Furthermore, as discussed below, consideration of the Wands factors demonstrates that the scope of the claims, teachings in the specification, knowledge of those of skill in the art, level of those of skill in the art and predictability in view of the data evidence that the specification teaches one of skill in the art to practice the method as claimed.

B. THE REJECTION OF CLAIMS 1 and 3-5 UNDER 35 U.S.C. §112, FIRST PARAGRAPH – SCOPE OF ENABLEMENT

Claims 1, 3-5 are rejected under 35 U.S.C. §112, first paragraph for being broader than the enabling disclosure. The Examiner alleges that the specification, while being enabling for the treatment of colon/colorectal tumors whose growth is stimulated by glycine-extended gastrin-17, does not reasonably provide enablement for 1) a method for the treatment of gastrointestinal tumors whose growth is stimulated by glycine-extended gastrin-17; 2) wherein the gastrointestinal tumors contain “CCCB-receptors;” and 3) wherein amidated gastrin-17 is inhibited.

In view of the amendments here, the rejection is moot with respect to 3). The amendment to claim 1 should not be construed that Applicant agrees with the Examiner's rejection. Applicant does not agree, and has amended the claims only for the purposes of advancing prosecution. As discussed below, the specification teaches that the anti-G17 antibody can neutralize amidated gastrin-17, and further teaches the amount of antibody titer that would be necessary to neutralize glycine-extended gastrin-17 and amidated gastrin-17 (see original claim 2, and specification, for example, at page 10, line 2-5). Also, as discussed below, antibodies were known and available in the art to assess the presence of amidated gastrin-17 to determine if it had been neutralized.

The rejection as to 1) and 2) above is respectfully traversed. It appears, however, that the Examiner means CCK-B receptors, and not CCCB receptors as set forth in the Office Action. The law regarding enablement is set forth above and not repeated here.

Preliminary Remarks

It appears that the Examiner is reading the claims to encompass all gastrointestinal tumors. They do not. The claims are directed to those gastrointestinal tumors that express glycine-extended gastrin-17, and in some cases, also contain CCK-B receptors. Hence, the methods are directed to a subset of gastrointestinal tumors. As discussed in detail below, the specification teaches how to identify such tumors, such that in combination with what is known

to one of skill in the art, the scope of the claims, the level of skill of those in the art, the predictability, particularly in light of the prior art and teachings in the specification, it would not require undue experimentation to practice the method as claimed.

Analysis

The inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require undue experimentation to make and use the claimed invention. As discussed in detail below, a consideration of the factors enumerated In re Wands demonstrates that the application, in conjunction with what was known to one of skill in the art as well as other factors, teaches how to make and use the full scope of the claimed subject matter.

Summary

The claims require that the gastrointestinal tumors express glycine-extended gastrin-17, and in some cases, also express the CCKB receptor. These and other teachings are provided in the specification and are known to the skilled artisan, as discussed in detail below, and any necessary adjustment can be determined empirically using routine testing. The application teaches a method for treating a subset of gastrointestinal tumors that *express* glycine-extended gastrin-17 with anti-G17 immunogens in an amount that is sufficient to neutralize the effects of gastrin-17 and glycine-extended gastrin-17. Further, the specification exemplifies the methods in a recognized rodent tumor model. The specification demonstrates effectiveness in the rat model implanted with DHDK12 tumors, a colon/colorectal tumor. The Examples show that the cells express glycine-extended gastrin and show antibody titer following administration. The specification also teaches assays for assessing neutralization of gastrin-17 and glycine-extended gastrin-17. The level of skill in the art is recognized to be high. The prior art, including the cited U.S. Patent No. 5,785,970 and other art, evidence that anti-G17 immunogens can be used to treat gastrointestinal tumors *per se*, it would not require undue experimentation to assess *any* gastrointestinal tumor for expression of glycine-extended gastrin-17 (and CCKB receptor) and administer an anti-G17 immunogen in an amount that is sufficient to generate antibody titers to inhibit not only gastrin but also glycine-extended gastrin-17. Thus, it would not require undue experimentation to perform a method that is within the scope of the claims, in view of the knowledge and level of skill in the art and the teachings and disclosure in the specification regarding methods for administering anti-G17 immunogens to gastrointestinal tumors that express glycine-extended gastrin-17.

1. The scope of the claims

Independent claim 1 is directed to a method for treatment of gastrointestinal tumors that express glycine-extended gastrin-17 by administering an anti-G17 immunogen in an amount that is sufficient to neutralize gastrin-17 and glycine-extended gastrin-17. Dependent claims recite particulars regarding the method. For example, claim 3 recites that the gastrointestinal tumors contain CCK-B receptors. Hence, the claims are directed to treating a subset of gastrointestinal tumors that express glycine-extended gastrin-17, and in some instances also CCK-B receptors. The claims are clearly within the scope of what is taught in the specification, i.e. treatment of gastrointestinal tumors that express glycine-extended gastrin-17 with anti-G17 immunogens in an amount that is sufficient to generate an immune response to neutralize gastrin-17 and glycine-extended gastrin-17.

2. Level of skill

As noted above, the level of skill in this art is recognized to be high (see, *e.g.*, Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'l 1986)). The numerous articles and patents made of record in this application address a highly skilled audience and further evidence the high level of skill in this art. Therefore, Applicant respectfully submits that using the teachings of the specification, one of skill in the art, could apply such teachings to any gastrointestinal tumor based on its expression of glycine-extended gastrin-17.

3. Teachings in the Specification and Working Examples

Applicant respectfully submits that the method as claimed is taught in the application, including in the Working Examples. The specification teaches that the methods can be used to treat gastrointestinal cancers that are affected by the prohormone glycine-extended gastrin-17, and teaches how to identify such cancers. For example, the specification teaches that a serum sample from a patient having a gastrointestinal cancer can be assayed to determine the expression and level of glycine-extended gastrin-17 in the blood (see *e.g.*, page 9, lines 13-15). In addition, the Examples show that radioimmunoassay of cancer cells can be performed to determine whether the tumor expresses glycine-extended gastrin-17. For example, Example 2 exemplifies a radioimmune assay for precursor gastrin levels in the rat colonic cell line DHDK12.

The specification further teaches that the methods can be performed on any such gastrointestinal cancer identified to be trophic due to the presence of the glycine-extended

gastrin-17 by administration of an immunogen capable of generating an immune response, e.g., antibody titer, that is sufficient to neutralize gastrin-17 and glycine-extended gastrin-17. The specification also describes assays to assess whether the amount of immunogen administered is sufficient to elicit antibody titers against gastrin-17 and glycine-extended gastrin-17. For example, the specification teaches that the antibody titer levels against glycine-extended gastrin-17 can be monitored from blood of a patient following administration of an anti-G17 immunogen, and that if necessary booster immunizations can be given, to ensure that such forms of gastrin have been neutralized by the treatment (see e.g., page 9, line 20 to page 10, line 2). The specification teaches the effective antibody titer necessary to neutralize both gastrin-17 and glycine-extended gastrin-17 (see e.g., page 10, lines 2-5). The specification also teaches monitoring of glycine-extended gastrin-17 in the serum to determine if it glycine-extended gastrin-17 is neutralized (see e.g., page 10, lines 5-6). The Examples further demonstrate that the tumor cells themselves can be assessed for expression of the precursor form after administration of the immunogen. Example 2, for example, describes the monitoring of the colon cancer cell line DHDK12 for the expression of glycine-extended gastrin-17 after administration of an anti-G17 immunogen.

The specification also teaches that a subset of gastrointestinal tumors express CCK-B receptors. For example, the specification cites a study by Upp *et al.* (Cancer Res. (1989) 49:488-492) that shows that 56.7% of human primary colorectal tumors express CCK-B receptors.

The Working Examples exemplify the method by administration of an anti-G17 immunogen to animals having a colon/colorectal tumor that express glycine-extended gastrin-17. For example, Example 1 depicts expression of glycine-extended gastrin-17 in the DHDK12 cell line. Example 2 demonstrates that treatment of those cells in vitro with an anti-G17 immunogen results in a reduction in the levels of glycine-extended gastrin-17 to levels that were undetectable by the radioimmunoassay procedure using antibodies specific for glycine-extended gastrin-17. Example 3 demonstrates that rats implanted with DHDK12 tumors, when administered anti-G17 immunogens, had a decreased growth of the tumors compared to control treatment. Example 4 shows results of the assessment of antibody titers elicited by the anti-G17 immunogen when administered to the rats implanted with the DHDK12 tumors. The results show that the antibody titers elicited were in excess of that able to bind to gastrin-17, and that there was free anti-G17(1-9)DT antibody levels measured, which increased with successive immunization with the

immunogen. This Example demonstrates that the amount of the anti-G17 immunogen administered was sufficient to generate antibody titers in excess of that able to bind gastrin-17, and that the antibody levels elicited could be controlled and monitored following further immunizations.

Examples 6 and 7 depict analysis of expression of the CCK-B receptor on the DHDK12 tumors by immunocytochemical evaluation using a polyclonal serum to the CCK-B receptor. The results show that the DHDK12 tumors have a high level of expression of the CCK-B receptor.

Accordingly, the application details methods of treatment of gastrointestinal cancers generally, and exemplifies the method with respect to colon/colorectal cancer. The specification teaches methods of assessing a patient having any gastrointestinal cancer for expression of glycine-extended gastrin-17 and CCK-B receptors, and methods of assessing and monitoring the immune response following administration of an anti-G17 immunogen such that the immunogen is administered in an amount that is sufficient to elicit an immune response to both gastrin-17 and glycine-extended gastrin-17. Such teachings adequately enable one of skill in the art to perform the method as claimed.

Additionally, Applicant is not required to teach what is well known in the art. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). Thus, it is sufficient if one of skill in the art can make and use the claimed subject matter using the teachings of the specification coupled with information known in the art MPEP §2164.01. By following these teachings, one of skill in the art can identify a mammal having a gastrointestinal cancer that expresses glycine-extended gastrin-17. Furthermore, at the time of the effective filing date of this application, there was a great deal of knowledge in the art regarding gastrin and its forms, gastrin-17 immunogens and specific anti-gastrin-17 antibodies, as well as methods to monitor tumors and other samples for specific protein markers of interest, such that by following the teachings of the specification those of skill in the art could readily identify a subset of patients having gastrointestinal tumors that express glycine-extended gastrin-17.

4. State of the prior art

At the time of filing of the application, a broad body of knowledge, including many references cited in the instant application, had amassed regarding the function of gastrin and its involvement in cancer etiology, including gastrointestinal tumors. In addition, much was known

regarding molecular biology techniques, and other techniques to detect proteins from various sources, in particular glycine-extended gastrin-17 and other gastrin forms, using a variety of techniques including, but not limited to, radioimmunoassay, immunohistochemistry, ELISA, and RT-PCR. For example, antibodies were available to glycine-extended gastrin-17 and were used to detect glycine-extended gastrin-17 from various sources (see e.g., Nemeth *et al.* (1995) *Gut*, 34:90-95; Singh *et al.* (1994) *Am. J. Physiol.*, 266:459-468; Ciccotosto *et al.* (1995) *Gastroenterology*, 109:1142-1153). In addition, ligand binding assays and RT-PCR methods were known and available to assess the presence of CCK-B receptors (see e.g., Povoski *et al.* (1994) *Am J Surg.* 167:120-126; Smith *et al.* (1993) *Am J Physiol.*, 265:149-155; Upp *et al.* (1989) *Cancer Res.*, 49:488-492). Hence, at the time of filing the application, one of skill in the art would know how to practice the method as claimed.

For example, at the time of filing the application, it was known in numerous references, many of which are cited in the application, that glycine-extended gastrin-17 was expressed in a subset of gastrointestinal tumors. For example, Nemeth *et al.* (*Gut* (1995) 34:90-95) describes the analysis of primary colorectal tumor extracts for the expression of gastrin forms, including glycine-extended gastrin-17. Nemeth *et al.* describes the operative and extraction procedures to determine expression of the gastrin forms in the tumors. Nemeth *et al.* also describes antibodies specific for various forms of gastrin, including progastrin, glycine-extended gastrin-17 and gastrin-17, and the use of such antibodies in radioimmunoassay to detect and quantify immunoreactivity. For example, in the study by Nemeth *et al.* 20 out of 44 tumors were reactive with the antibody to glycine-extended gastrin-17, a subset of all tumors assessed. Singh *et al.* (*Am. J. Physiol.* (1994) 266:459-468) describes studies measuring the concentration of precursor forms of gastrin in colon cancer cell lines using specific antibodies, and the stimulatory effect of glycine-extended gastrin-17 on tumor cell growth. In the studies of Singh *et al.*, glycine-extended gastrin-17 was measured in all the mouse and human colon cancer samples tested (HCT-116, MC-26, COLO 205 and DLD-1). Further, the studies of Singh *et al.* show that glycine-extended gastrin-17 stimulates growth of DLD-1 cells and therefore is mitogenic for colon cancer cells. In another study, Ciccotosto *et al.* (*Gastroenterology* (1995) 109:1142-1153) describes the analysis of tumor extracts from patients with colorectal carcinoma by radioimmunoassay using an antibodies to various forms of gastrin. In the study, glycine-extended gastrin-17 was detected in 44% of the resected tumors. It also was known at the time

of filing the instant application that glycine-extended gastrin-17 stimulates the growth of tumor cells, including pancreatic and intestinal cell lines (see e.g., Seva *et al.* (1994) *Science*, 265:410-412; Singh *et al.* (1995) *J Biol. Chem.*, 270: 8429-8438).

These references to numerous published information and protocols regarding tumor extraction and manipulation to assess expression of gastrin forms, including glycine-extended gastrin-17, and the availability of antibodies that specifically recognize glycine-extended gastrin-17 demonstrate the large volume of information regarding tested and reliable procedures available at the time of filing of the instant application. This evidences the advanced state of the art at the relevant time and the availability of such procedures to practice the method as claimed.

5. The quantity of experimentation

The quantity of experimentation to identify whether a gastrointestinal tumor expresses glycine-extended gastrin-17 and also CCK-B receptors (claim 3) is minimal. For example, assays are known and antibodies were available at the time of filing of the application, to specifically identify whether glycine-extended gastrin-17 is expressed in the blood or tumor of a patient having a gastrointestinal cancer. Such experiments are routine. The application describes assaying for glycine-extended gastrin-17. The claims require administering an gastrin-17 immunogen. As noted above, such immunogens are known; so no experimentation is need. The amount to be administered is sufficient to elicit an antibody titer sufficient to neutralize gastrin-17 and glycine-extended gastrin-17. As note assays for determining glycine-extended gastrin-17, and gastrin-17 are known. Treatment of tumors by neutralizing gastrin-17 is known. Hence little experimentation is required.

6. Predictability

The specification describes anti-G17 immunogens and the use of such immunogens to treat gastrointestinal tumors that express glycine-extended gastrin-17 to neutralize gastrin and glycine-extended gastrin-17 so as to inhibit the trophic effects of these hormones on tumor cells. The specification provides data from recognized animal models evidencing that the immunogens neutralize both species and treat tumors. Assays to assess expression of glycine-extended gastrin-17 were described in the specification, and known to one of skill in the art. Assays also were known in the art and described in the specification to determine if a tumor contains CCK-B receptor. Further, the specification includes Working Examples to show that administration of an anti-G17 immunogen, in an amount sufficient to induce antibody titers in excess of antibodies

required to bind to serum-associated G17, to an animal having tumors expressing glycine-extended gastrin-17 resulted in reduction in tumor size. Hence, the specification, and the state of the prior art, demonstrate the predictability of the method as claimed in accord with the teachings of the specification.

Conclusion

Therefore, in view of the scope of the claims, teachings in the specifications, working examples, level of skill in the art, predictability, knowledge of those of skill in the art, it would not require undue experimentation to practice the claimed method. As noted above, the claims are directed to method detailed in the specification; the level of skill in the art is high, the knowledge of those of skill in the art is high, the amount of experimentation, if any, is routine, and the results of practice of the method are predictable.

Fairness

Applicant is entitled to claims that are commensurate in scope with not only with what applicant has specifically described and exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed. In this instance, applicant has disclosed and taught methods for treatment of gastrointestinal tumors express glycine extended gastrin-17. It is unfair and unduly limiting to require applicants to limit the claims, when the application clearly teaches how to practice the method as claimed. The specification clearly places those of skill in the art in possession of the method as claimed; the specification teaches that tumors express glycine extended gastrin-17, how to identify such tumors, and how treat such tumors, including how to assess dosages. To limit the claims to treatment of only colon/colorectal tumors whose growth is stimulated by glycine-extended gastrin-17, rather than to any gastrointestinal tumor, is a contrary to the public policy upon which the U.S. patent laws are based to require applicant to limit the claims. See, for example, *In re Goffe*, 542 F.2d 801, 166 USPQ 85 (CCPA 1970):

for the Board to limit appellant to claims involving the specific materials disclosed in the examples so that a competitor seeking to avoid infringing the claims can merely follow the disclosure and make routine substitutions "is contrary to the purpose for which the patent system exists - to promote progress in the useful arts."

The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the disclosure. This requires as much the granting of broad claims

on broad inventions as it does the granting of more specific claims on more specific inventions. *In re Sus and Schafer*, 49 CCPA 1301, 306 F.2d 494, 134 USPQ 301, at 304. If applicant is required to limit the claims as suggested by the Examiner, then those of skill in the art can, by virtue of the teachings of this application, treat any gastrointestinal tumor other than a colon/colorectal tumor, that express glycine-extended gastrin-17 by practicing what is disclosed in the application, and avoid infringing claims so-limited. The instant application teaches a broader modality; and having done so, places the public in possession of such knowledge. Having provided this disclosure, it permits others to benefit therefrom. Those of skill in the art should not be permitted to practice what is taught in the application, but avoid infringing the claims. To permit that is simply not fair. Inventors and their companies can ill-afford to dedicate their innovations to the public.

Rebuttal

1) The Examiner cites Dufresne *et al.* (Physiological Reviews, 2006, 86: 805-847) to urge that the only disclosure in the art of glycine-extended gastrin-17 associated with any tumor is in reference to colon tumors, and that therefore, neither this teaching nor the teaching of the specification provides enabling support that would point to any other gastrointestinal tumor type that could be treated with a reasonable expectation of success by the broadly claimed method. Applicant respectfully disagrees.

First, reasonable expectation of success is not the standard with respect to scope of enablement. Second, it is respectfully submitted that it is not necessary to know ahead of time the identity all gastrointestinal tumors that express glycine-extended gastrin-17 to practice the method as claimed without undue experimentation. The specification teaches that gastrointestinal tumors expressing glycine-extended gastrin-17 can be identified, for example, by assaying the serum or tumor for glycine-extended gastrin-17, such as by radioimmunoassay. Such a determination is routine. Antibodies specific to glycine-extended gastrin-17 were known as of the effective filing date, and are taught in the specification. Hence, the method is directed to treating a subset of gastrointestinal tumors that express glycine-extended gastrin-17. Tumors that fall into this class, if not known, can be readily identified.

Furthermore, it respectfully is submitted that the reference of Dufresne *et al.* is directed to a review of *receptors* to gastrin and cyolecystokinin, not to gastrin hormones per se. Hence, the Examiner premising of a rejection based on this reference is misplaced. It is unclear how this

reference can be considered to be a complete review of the state of the art of gastrin hormones, including glycine-extended gastrin-17, nor does the reference teach that one of skill (in 1996) in the art *in light of the instant application* could not identify a tumor that expresses glycine-extended gastrin-17. There is nothing in the reference that would suggest that one could not do so.

2) With respect to the rejection of claim 3, it respectfully is submitted that is directed to a method of treating a gastrointestinal tumor of claim 1, where the tumors also contain the CCK-B receptor. There is no requirement in the claimed method that glycine-extended gastrin-17 interact with these receptors; the claim is further defining a species of tumor: those that express glycine-extended gastrin-17 and also contain CCK-B receptor. One of skill in the art can easily assess and determine whether a gastrointestinal tumor expresses glycine extended-gastrin-17 and contains the CCK-B receptor. The specification teaches this, and assays were known to one of skill in the art to measure levels of the hormone and receptor. The claims do not require that glycine-extended gastrin-17 stimulate the tumor cells through the CCK-B receptor. The exemplified tumor is one that expresses glycine-extended gastrin-17 and CCK-B receptor. Hence it is unclear why the Examiner urges that this limitation is unpredictable, since the working example provides an example, and the specification teaches how to identify such tumors.

Again, Applicant reminds the Examiner that it is irrelevant that not all gastrointestinal tumors express CCK-B receptors. The claims limit the method to treatment of gastrointestinal tumors that express glycine-extended gastrin-17, and in some cases also CCK-B receptors, and hence claim 3 is directed to treatment of gastrointestinal tumors that express glycine-extended gastrin-17 and CCK-B receptor.

The Examiner cites a number of references that allegedly show that it is unpredictable which colorectal carcinomas express CCK-B (see *e.g.*, Baldwin *et al.* (1998), 42:581-584; Dufresne *et al.*). These references, however, rather than supporting the Examiner's assertion, It show that some colorectal carcinomas/tumors express CCK-B. For example, Baldwin *et al.* cites the study of Upp *et al.* (also cited in the instant application) that shows that 57% of colorectal carcinomas tested contain high affinity CCK-B receptors. In addition, Dufresne *et al.* summarizes that CCK2R (i.e. CCK-B) is expressed and found in gastrointestinal tumors, including pancreatic carcinoma, esophageal adenocarcinoma and in a minority of colon cancers.

3) In addition, it respectfully is submitted that analysis of enablement requires consideration of all of the "Wands Factors;" focusing on one or two is a misapplication of the law. All factors must be considered and weighed. A deficiency in meeting one factor does not preclude a finding of enablement. In the instant case, the Examiner only urges that the application is not enabled based on a single reference in view of the teachings of the specification. It is noted that what is known in the art is greater than a single reference, and also that the teachings in the specification is only one factor that should be considered. Further, the specification does teach how to practice the method as claimed, including working examples demonstrating its effectiveness. The claimed subject matter is directed to administration of an anti-G17 gastrin immunogen for treatment of gastrointestinal tumors that express glycine-extended gastrin-17. Given the teachings of the specification, presence of working examples, the state of the prior art, the scope of the claims, the knowledge of those of skill in the art, and the high level of skill in the art, one of skill in the art can identify mammals having gastrointestinal tumors that express glycine-extended gastrin-17 to practice the methods as claimed without undue experimentation.

III. THE REJECTION OF CLAIMS 1, 3-5 UNDER §112, FIRST PARAGRAPH – WRITTEN DESCRIPTION -Possession

Claims 1, 3-5 are rejected under 35 U.S.C. §112, first paragraph for lack of written description because it is alleged that the specification fails to sufficiently describe glycine-extended gastrin-17 stimulated gastrointestinal tumors by either the test set out in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) (Lilly) or in Enzo Biochem, Inc. v. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002) (Enzo). Specifically, the Examiner urges that, while the specification describes a "hypothesized glycine-extended gastrin-17 stimulated gastrointestinal tumor," it fails to describe a "representative number" of such species, and does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Accordingly, the Examiner alleges that the specification does not provide an adequate written description of the glycine-extended gastrin-17 stimulated gastrointestinal tumors that is required to practice the claimed invention, and thus fails to describe the method of treatment.

This rejection respectfully is traversed. Review of the law reveals that the Examiner has not demonstrated that the Applicant did not have possession of the method as claimed, including

a method of administering an anti-G17 immunogen to treat gastrointestinal tumors expressing glycine-extended gastrin-17, at the time of filing of the application.

Relevant Law

The purpose behind the written description requirement is to ensure that the patent applicant had possession of the claimed subject matter at the time of filing of the application In re Wertheim, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure.

35 U.S.C. §112 requires a written description of the invention. This requirement is distinct from and not coterminous with the enablement requirement:

The purpose of the ‘written description’ requirement is broader than to merely explain how to ‘make and use’; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the ‘written description’ inquiry, whatever is now claimed.” Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563-64, 19 USPQ2d at 1117 (emphasis in original).

The issue with respect to 35 U.S.C. §112, first paragraph, adequate written description has been stated as:

[d]oes the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific compound [claimed embodiment] Vas-Cath, Inc. v. Mahurkar, at 1115, quoting In re Ruschig, 390 F.2d 1990, at 995-996, 154 USPQ 118 at 123 (CCPA 1967).

A specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.*, whatever is now claimed. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). A written description requirement issue generally involves the question of whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon “reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter.” Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)) (see also, MPEP 2163.02).

An objective standard for determining compliance with the written description requirement is “does the description clearly allow persons of skill in the art to recognize that he

or she invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ.2d 1614, 1618 (Fed. Cir. 1989).

The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. In re Wertheim, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976); *See also Ex parte Sorenson*, 3 USPQ.2d 1462, 1463 (Bd. Pat.App. & Inter. 1987). By disclosing in a parent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter. In re Reynolds, 443, F.2d 384, 170 USPQ 94 (CCPA 1971); and In re Smythe, 480 F.2d 1376, 178 USPQ 279 (CCPA 1973).

The Federal Circuit has discussed the application of the written description requirement of the first paragraph of 112 to claims in the field of biotechnology. See *University of California v. Eli and Co.*, 1 19 1559, 43 1398, 1406 (Fed. Cir. 1997). The court explained that:

In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus . . . a generic statement such as "vertebrate insulin or "mammalian insulin without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

The court also stated that "[a]written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or]chemical name, 'of the claimed subject matter sufficient to distinguish it from other materials." at 1567, 43 at 1405. Finally, the court addressed the manner by which a genus of might be described. "A description of a genus of may be achieved by means of a recitation of a representative number of defined by nucleotide sequence, falling within the scope

of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The Federal Circuit also has addressed the written description requirement in the context of biotechnology-related subject matter in *Enzo Biochem. Inc. v. Gen-Probe* 296 F.3d 63, 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that:

the written description requirement can be met by 'showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . complete or partial structure, other physical chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.' [Emphasis added] at 3

The court in Enzo adopted its standard from the Written Description Examination Guidelines. 296 at 1324, 63 at 3 (citing the Guidelines).

It is well-settled that the written description requirement of 35 U. S. C. §112, first paragraph, can be satisfied without express or explicit disclosure of a later-claimed invention. See, *In re Herschler*, 591 F.2d 700, 200 USPQ 711, 717 (CCPA 1979): "The claimed subject matter need not be described in *haec verba* to satisfy the description requirement. It is not necessary that the application describe the claim limitations exactly, but only so clearly that one having ordinary skill in the pertinent art would recognize from the disclosure that appellants invented processes including those limitations." (citations omitted). See also *Purdue Pharma L. P. v. Faulding, Inc.*, 230 F.3d 1320, 1323, 56 F.3d 1481, 1483 (Fed. Cir. 2000) In order to satisfy the written description requirement, the disclosure as originally filed does not have to provide in *haec verba* support for the claimed subject matter at issue.".

The claims

The claims in the instant application, recite a method of treating gastrointestinal tumors that express glycine-extended gastrin-17, by administering an anti-G17 immunogen in an amount that is sufficient to neutralize gastrin-17 **and** glycine-extended gastrin-17. In particular, claim 1 recites:

A method for the treatment of gastrointestinal tumors, comprising:
administering to a mammal a therapeutically effective amount of an anti-G17 immunogenic composition, wherein:

the gastrointestinal tumor expresses glycine-extended gastrin-17; and
the amount of the immunogenic composition administered is sufficient to induce an anti-G17 antibody titer to neutralize gastrin-17 and glycine-extended gastrin-17.

Dependent claims 3-5 recite particulars of the method. For example, claim 3 recites that the gastrointestinal tumors contain CCK-B receptors. Claim 4 recites that the gastrointestinal tumors are colorectal adenocarcinomas. Claim 5 recites that the mammal is a human.

Analysis

To satisfy the written description requirement, it is not necessary for the application to describe the claim limitations exactly, but only so clearly that one having skill in the pertinent art would recognize from the disclosure that an applicant invented the claimed subject matter. Thus, the fact that the specification describes only one example of a gastrointestinal tumor that expresses glycine-extended gastrin-17 (and CCK-B receptors), and does not list other species of such gastrointestinal tumors, is not dispositive of the written description issue. The Enzo court stated that "the written description requirement can be met by showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics... complete or partial structure, other physical chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Further, the Lilly court stated that written description can be satisfied by a showing of "structural features commonly possessed by members of the genus that distinguish them from others."

This standard is met. The specification specifically describes that a gastrointestinal tumor of the method is one that expresses glycine-extended gastrin-17. There is no requirement to disclose every species encompassed within the claimed genus. In this instance, the specification defines structural features of the genus of gastrointestinal tumors treated based on the expression of glycine-extended gastrin-17. Such description includes description regarding assays to identify such gastrointestinal tumors that express glycine-extended gastrin-17, for example, by assaying a serum sample from a patient having a gastrointestinal cancer for glycine-extended gastrin-17 or performing a radioimmunoassay on the tumor cells. Accordingly, since the structural feature of the claimed gastrointestinal tumors that express glycine-extended gastrin-17 is described in the specification, one of skill in the art using routine methods can identify any number of species of such gastrointestinal tumors. Hence, there is no need for the specification to set forth all of the claimed gastrointestinal tumors on which the method can be practiced. If necessary, one of skill in the art could assay for glycine-extended gastrin-17 in the

serum or tumor of a mammal as described in the specification to identify those within the scope of the claim.

Furthermore, the claims are drawn to a *method* of treating gastrointestinal cancers that express glycine-extended gastrin-17 by administering an anti-G17 immunogen, not to the gastrointestinal tumors per se. Species of such gastrointestinal tumors that expressed glycine-extended gastrin-17 **were known** in the art as of the effective filing date (see e.g., Nemeth *et al.* (1995) *Gut*, 34:90-95; Singh *et al.* (1994) *Am. J. Physiol.*, 266:459-468; Ciccotosto *et al.* (1995) *Gastroenterology*, 109:1142-1153).

Thus, one of skill in the art would have recognized from reading the disclosure that the inventors had possession of the method as claimed, including administration of an anti-G17 immunogen to treat a mammal having a gastrointestinal tumor expressing glycine-extended gastrin-17 at least at the time of filing of the application. This teaching and knowledge, coupled with the ability to assay for species of such gastrointestinal tumors using assays provided in the specification and what was known in the art, demonstrates that Applicant sufficiently described and was in possession of method as claimed.

IV. THE REJECTION OF CLAIMS 1, 3-5 UNDER §112, FIRST PARAGRAPH- NEW MATTER

Claims 1, 3-5 are rejected under 35 U.S.C. §112, first paragraph for lack of written description because it is alleged that there is no disclosure of inhibiting the physiological effects of amidated gastrin-17, and that the subject matter of the claims broadens the scope of the invention as originally disclosed in the specification. Applicant respectfully traverses this rejection.

It appears that this is a new matter rejection, and that the Examiner is urging that the claims lack support for the limitation that an amount of immunogen administered is sufficient to inhibit physiological effects of gastrin-17, amidated gastrin-17 and glycine-extended gastrin-17. Although this rejection is moot by amendment of the claims herein, Applicant respectfully submits that the previously pending claims, and the claims as amended herein, are supported by the disclosure as originally filed. For example, the claims find support in original claim 2, which specifies that the immunogen administered induced anti-G17 antibodies of an effective titer in the immunized mammal that bind and neutralize amidated and glycine-extended gastrin-17.

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Preliminary Amendment and RCE

Applicant respectfully disagrees for reasons discussed below. Nevertheless, this rejection is moot in view of the amendment of claim 1 herein.

Basis for claim 1 can be found in the specification as originally filed. For example, the specification at page 5, beginning at line 4 recites as follows:

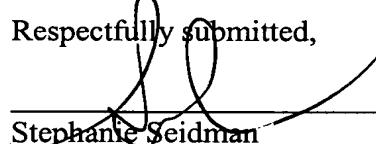
In one embodiment of the invention, the method of immunization against amidated or glycine-extended G17 comprises active immunization, wherein a patient is immunized with an immunogen of the invention. The immunogen stimulates the production of antibodies against amidated and glycine-extended G17 in the immunized patient, inducing sufficient antibody titers to neutralize and inhibit the physiological effects of amidated and glycine-extended G17 so as to limit the cancer-trophic hormone levels produced by the patient.

Additional support can be found at the specification, for example, at page 8, lines 17-18; at page 9, line 15 to page 10, line 5. Furthermore, the original claims recited treatment of tumors that express amidated gastrin-17.

Accordingly, recitation of amidated gastrin-17 in claim 1 as previously amended did not add new matter. As noted, however, this language has been cancelled from the claims as amended herein, thereby rendering this rejection moot.

* * *

In view of the, amendments and remarks herein, reexamination and allowance of the application are respectfully requested.

Respectfully submitted,


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